Association Between Liver Fibrosis and Serum Prostate Specific Antigen (PSA) Among US Men: Findings from National Health and Nutrition Examination Survey (NHANES) 2001–2010

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A thesis submitted to The Johns Hopkins University in conformity with the requirements for the degree of Master of Science

Baltimore, Maryland April 2018

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ABSTRACT

Importance Some studies have observed that men with liver cirrhosis have lower serum prostate specific antigen (PSA) concentration, which could delay the detection of an occult prostate cancer. Yet, no previous study has examined the association of liver function and advanced fibrosis with serum PSA level in a US nationally representative sample of men.

Objective To evaluate the association of liver fibrosis scores with PSA level among men aged older than 40 years in the overall US population and among non-Hispanic White, non-Hispanic Black, and Mexican-American or other Hispanic men.

Design, Setting and Participants Data from the 2001 to 2010 continuous National Health and Nutrition Examination Survey (NHANES) were used. Males aged 40 years and over without a diagnosis of prostate cancer and who had serum PSA, liver enzymes (aspartate transaminase [AST], alanine aminotransferase [ALT]), and albumin concentrations, and platelet counts measured as part of the NHANES protocol were included in this cross-sectional analysis.

Exposures Liver fibrosis was measured using three established, non-invasive fibrosis scores: AST to platelet ratio index (APRI), fibrosis 4 index (FIB-4) and NAFLD fibrosis score (NFS).

Main Outcomes and Measures We assessed the overall and race-stratified geometric mean PSA concentrations by categories of the liver fibrosis scores using predictive margins by multivariable linear regression, and the association of abnormal liver fibrosis scores (APRI>1, FIB-4 >2.67, NFS>0.676) and elevated PSA levels (>2ng/mL, >4ng/mL) by multivariable logistic regression. We adjusted for age, race/ethnicity, body mass index, diabetes status, alcohol drinking, and smoking.

Results Overall, 6,774 men were included in this study (mean age 55.1 years). Men with higher liver fibrosis scores had lower geometric mean PSA: APRI (p trend<0.001), FIB-4 (p trend=0.007) and NFS (p trend<0.001). After stratifying by race, this pattern remained among each race/ethnicity, though not statistically significant among non-Hispanic Black and Mexican-American/Other Hispanic men (both p trend>0.05). Men with abnormal liver fibrosis scores had a lower PSA compared with those without advanced liver fibrosis, which was also observed in each race/ethnicity group p <0.05). Moreover, regardless of

the race/ethnicity men with abnormal liver fibrosis scores had a lower odds of an elevated PSA level (e.g., defined by APRI: OR of PSA >2 ng/mL=0.67; OR of PSA >4 ng/mL=0.33).
Conclusions and Relevance In this US nationally representative study, men of all race/ethnicities with higher liver fibrosis scores had lower serum PSA concentration and men with advanced fibrosis scores had a lower odds of an elevated PSA, which could lower the probability of detecting asymptomatic prostate cancer. Given that early detection may be beneficial for prostate cancer treatment and survival and given that Black men are more likely to develop aggressive prostate cancer, a delayed diagnosis could contribute to the higher prostate cancer mortality among US Black men. As for any man, the risk and benefits of prostate cancer screening for men with diagnosed liver disease should be considered in decision-making.

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Thesis Reader: Dr. Mariana Lazo

ACKNOWLEDGEMENTS

First and foremost, I offer my sincerest gratitude to my academic and thesis advisor **Dr. Elizabeth A. Platz**. The door to Dr. Platz office was always open whenever I ran into a trouble spot or had a question about my research or writing. She consistently allowed this paper to be my own work, but steered me in the right the direction whenever she thought I needed it. More importantly, she also guided me to think epidemiology from a translational way, and to conduct research that can link scientific discovery closely to population health impact. It has been an honor and fortune for me to be her student.

I would also like to thank the **Dr. Mariana Lazo** who provided precious guidance for this research project from her expertize of liver disease and NHANES research. Without her passionate participation and input, the project could not have been successfully conducted.

Furthermore, I would like to acknowledge **Mr. John Barber** and **Dr. Michael Marrone** for their advice on the data analysis. I would like also to thank all the members in Dr. Platz's group. Without them, the thesis would not have been possible. They are all such nice, wise and patient persons to work with that I remain greatly appreciative.

Finally, I must express my very profound gratitude to my parents and to my peers at Epi cohort for providing me with unfailing support and continuous encouragement over the past two years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

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INTRODUCTION

Evidence from studies of cirrhotic patients links poor liver function to a reduction in serum prostate-specific antigen (PSA) concentration among men.[1-3] The liver plays a key role in both PSA production and clearance.[4] Reduced PSA clearance by an impaired liver could result in a higher serum PSA concentration. On the other hand, with chronic poor liver function, testosterone levels drop, which can result in a decline in the production of PSA, which is under androgenic regulation.[5,6] The usual PSA concentration for which biopsy is indicated is at >4 ng/mL. A shift in the distribution of PSA concentration toward a higher level could result in some men without prostate cancer being sent for an unnecessary biopsy. Alternatively, a shift in the distribution of PSA concentration toward lower levels could result in some men with yet undiagnosed prostate cancer from being detected with the disease while it is still asymptomatic. Moreover, the majority of PSA circulates bound to several proteins (alpha 1-antitrypsin, alpha 1-antichymotrypsin and alpha 2-macroglobulin); these proteins are synthesized by the liver.

Over the last 2 decades, PSA testing has been adopted for prostate cancer early detection throughout the US.[7] Lower PSA concentration at the time of screening may lead to a delay in detection of prostate cancer with a lethal phenotype. Black men experience profound disparity in metastatic and lethal prostate cancer rates compared with White men in the US.[8,9] According to the most recent statistics from American Cancer Society, the incidence of prostate cancer is 198.4 per 100,000 among non-Hispanic Black men, 114.8 per 100,000 among non-Hispanic White men, and 104.9 per 100,000 among the Hispanic/Latino men; the non-Hispanic Black men have a more than twice higher risk of dying from this disease than their White or Hispanic/Latino counterparts.[10] Meanwhile, previous studies in the US nationally representative National Health and Nutrition Examination Survey (NHANES) document that a racial disparity in certain types of liver diseases. For example, non-Hispanic Blacks had a higher prevalence of cirrhosis and infectious hepatitis [11-13], while nonalcoholic fatty liver disease (NAFLD) was more common in Mexican American. [14] The higher burden of liver diseases in certain subgroups, may help explain the racial disparities observed in the incidence of metastatic and lethal prostate cancer. Given that early detection may be beneficial for prostate cancer treatment and survival, a delayed diagnosis

of aggressive prostate cancer could contribute to the higher prostate cancer mortality among Black American men.[15]

Thus, in this study we determined the association between liver fibrosis scores and serum PSA concentration overall and by race/ethnicity in a nationally representative sample of men in the target age range for prostate cancer screening. We address this question to inform the likelihood of delay in the detection of prostate cancer in men with liver conditions and also whether the higher risk of prostate cancer death in Black men may be, in part, due to a higher prevalence of liver fibrosis and consequent influence on the tool used for the early detection of prostate cancer.

METHODS

Study Population

We used data from five cycles of Continuous NHANES (2001-2002, 2003-2004, 2005-2006, 2007-2008 and 2009-2010). NHANES is a US nationally representative survey that aims to provide knowledge on the health status of US population through collecting data from interviews, physical examinations, and laboratory measurements. The survey used a complex, multistage, probability design to select a study sample from the civilian, noninstitutionalized population with oversampling of non-Hispanic Blacks, Asians, Hispanic Americans, and persons aged 60 years or older. Use of sampling weights produces nationally representative estimates. Detailed study design, content, and procedures have been discussed in previous reports.[16] Written informed consents were obtained from all participants, and all protocols of NHANES studies implementation were under approval by the Research Ethics Review Board of the National Center for Health Statistics, US Centers for Disease Control and Prevention.

In our study, we restricted our analyses to male participants 40 years or older given that serum PSA levels were only measured among them. In addition, we excluded those with missing data on demographics (age and ethnicity) and clinical data (liver fibrosis scores biomarkers, body mass index (BMI), diabetes status, smoking, and alcohol drinking history, viral hepatitis). We further excluded from the analysis males with extreme BMI (<18.5 or >50 kg/m^2), with self-reported liver transplant, prostate cancer or liver cancer. The total analytical and unweighted sample size was n=6,705.

Measurement of PSA

As part of the NHANES protocol, from 2001 to 2010, serum total PSA concentration was measured by Hybritech immunoassay (Beckman Coulter, Fullerton, CA) for male participants aged 40 years and over [17]. PSA was not measured for men with a recent prostate biopsy, prostate infection or inflammation, rectal examination, or for men with a history of prostate cancer.

Assessment of liver fibrosis

As part of the NHANES protocol, biochemical markers related to liver function – aspartate aminotransferase (AST), alanine aminotransferase (ALT) – as well as albumin were measured using a Beckman Synchron LX20. In addition, platelet count was measured using the Beckman UniCel® DxC800 Synchron; detailed procedures are described elsewhere.[17] To assess liver fibrosis of participants, we estimated three non-invasive fibrosis scores: AST/platelet ratio index (APRI), fibrosis 4 index (FIB-4) and NAFLD fibrosis score (NFS). The APRI and FIB-4 indices were originally developed to predict fibrosis and cirrhosis among patients with hepatitis C[18,19] and have been validated in other chronic liver diseases in later studies to accurately identify patients with significant fibrosis.[20-23] Given its simplicity and validity, APRI is recommended by the World Health Organization to identify fibrosis stage in resource-constrained areas.[24] The NFS was developed to identify advanced fibrosis in patients with NAFLD and showed 0.84 of the area under the ROC curve.[25] The scores were calculated by following equations:

$$\text{APRI} = ((\text{AST [U/L]} / \text{upper limit of normal}) / \text{platelet count [}10^9\text{/L]}) \times 100 \quad (1)$$

$$\text{FIB-4} = (\text{Age [yrs]} \times \text{AST [U/L]}) / (\text{platelet count [}10^9\text{/L]} \times \text{ALT [U/L]}^{1/2}) \quad (2)$$

$$\text{NFS} = -1.675 + (0.037 \times \text{age [yrs]}) + (0.094 \times \text{BMI [kg/m}^2\text{]}) + (1.13 \times \text{impaired fasting glucose or diabetes}) + (0.99 \times \text{AST/ALT}) - (0.013 \times \text{platelet count [}10^9\text{/L]}) - (0.66 \times \text{albumin (g/dL)}) \quad (3)$$

In the formula above, BMI was calculated as weight (kg) divided by height (m) squared. Participant were defined as having impaired fasting glucose or a diagnosis of diabetes when their fasting glucose was >100 mg/dL or they responded yes to the question of whether a "Doctor told you have diabetes". [26] We used 33 U/L as upper-limit of normal of AST based on published NHANES ranges. [27] In our study, we defined abnormal fibrosis score as: APRI>1, FIB-4 >2.67 or NFS>0.676.[28,29]

Other covariates

As part of NHANES, information regarding age at survey, race/ethnicity, education level, drinking status, smoking history were collected by questionnaire. We categorized race/ethnicity was categorized as "Non-Hispanic White", "Non-Hispanic Black", "Mexican American or other Hispanic" and "other race". Participants' highest achieved

education level was classified into 5 groups: "less than 9th grade", "9-11th grade (includes 12th grade with no diploma)", "high school graduate/GED or equivalent", "some college or associate's degree" and "college graduate or above". Drinking status was estimated through the participants' self-reported average daily alcohol consumption and drinking frequency. Males who consumed ≥30 g alcohol per day were categorized as "heavy drinker", otherwise they were categorized as "non-heavy drinker". Men who reported current smoking or previous consumption of at least 100 cigarettes were categorized as "positive smoking history", otherwise they were categorized as "negative smoking history".

Using the CDC standard, men with a BMI ≥30 kg/m^2 were classified as "obese"[30], otherwise, they were classified as "normal/overweight". We classified men with respect to diabetes status and glycemia control: men who did not report a diagnosis of diabetes and had glycated hemoglobin <5.7% were classified as "no diabetes"; men who did not report a diagnosis of diabetes and had a glycated hemoglobin of 5.7%-6.4% were classified as "at risk for diabetes"; men who reported a diagnosis of diabetes and had a glycated hemoglobin of <7% were classified as "controlled diabetes"; men with a diagnosis of diabetes and who had a glycated hemoglobin ≥7% or men without a diagnosis of diabetes but who had a glycated hemoglobin >6.4% were classified as "uncontrolled diabetes".[31]

Self-reported liver disease was obtained through the question "Has a doctor or other health professional ever told you had any kind of liver condition?" Liver condition included viral hepatitis, NAFLD, liver cancer, etc. Hepatitis B and C testing were performed and among NHANES participants. We considered participants with positive result of hepatitis C antibody (anti-HCV) test as HCV infected. Participants tested positive for hepatitis B core antibody (anti-HBc) were considered as with current or previous HBV infection and those tested positive for hepatitis B surface antigen (HBsAg) were considered as with chronic HBV infection. HBsAg was only tested if one showed positive in Anti-HBc. The laboratory process of has been discussed elsewhere. [13,32]

Statistical analysis

To account for the clustered design and differential sampling probabilities, sample weights that reflect the probability of selection and response were used in the analysis to produce unbiased national estimates and the Taylor linearization method and the masked variance

units (MVU) were used for variance estimation to account for the complex NHANES sample design. Participant characteristics were compared by normal/abnormal fibrosis score and by PSA level (<1, 1- 2, 2-4, 4-10, ≥10 ng/mL); PSA> 4ng/mL is the typically clinical cut-point for referring to prostate biopsy.

The PSA concentration was transformed using the natural logarithm to achieve a normal distribution for further analyses. Overall and race-stratified geometric mean PSA concentration and 95% confidence intervals (CIs) were estimated using predictive margins (model-based standardization) from multivariable linear regression. In the regression models, we entered quintiles of each fibrosis score or clinical categories (normal vs. abnormal). P-trends were estimated using linear regression with the median of each fibrosis score category as continuous variable to capture the direction of the association between liver function score and PSA concentration. Logistic regression was used to estimate the odds ratio (OR) of higher PSA level (>2, >4, or >10 ng/mL) associated with abnormal liver fibrosis scores.

We also conducted sensitivity analyses by restricting to males with BMI <30 kg/m^2, males without a diagnosis of diabetes or a glycated hemoglobin >6.4%, males with self-reported liver disease, males with self-reported liver disease and/or current or previous viral hepatitis, and males with self-reported liver disease and/or chronic viral hepatitis respectively. We re-classified abnormal/normal fibrosis score by creating an indicator of the number of abnormal APRI, FIB-4 and NFS scores, and analyzed the association between the joint indicator and elevated PSA concentration through logistic regression.

All p-values were 2 tailed and $p<0.05$ was used as the threshold for statistical significance. All statistical analyses were carried out using STATA 14.2 for Windows statistical software package.

RESULTS

Study Population Characteristics

Table 1 compares weighted general characteristics by fibrosis scores. Based on different fibrosis scores, 2.1% males had abnormal APRI score, 3.6% males had abnormal FIB-4 score, and 5.6% males had abnormal NFS score. The proportions slightly differed by race (proportions of abnormal fibrosis score defined by APRI, FIB-4 and NFS: 1.8%, 3.6% and 5.8% in non-Hispanic Whites; 3.5%, 4.5% and 5.4% in non-Hispanic Blacks; 2.8%, 2.7% and 3.9% in Mexican American/other Hispanics). The mean age of the overall participants was 55.1 years. In general, the men with abnormal score tended to be older, to be non-Hispanic White, to have a lower educational level, to be heavy drinkers, to have ever smoked, to be obese, to have diabetes or prediabetes, to have self-reported liver disease, and to have HCV or HBV infection. In Table 2, we examined the general characteristics of the men by categories of PSA concentration. PSA levels increased with age, and as serum PSA concentration increased, the proportion of men who are non-Hispanic Black, who have a lower educational level, or who were current or previous HBV infected increased, while the proportion of men with obesity, with self-reported liver disease, or with HCV infection decreased.

Liver fibrosis scores and geometric mean PSA

The figures show the age-adjusted association between fibrosis scores and geometric mean PSA concentration. Geometric mean PSA decreased with increasing APRI, FIB-4, and NFS scores (Figure 1.A-C). After dividing fibrosis scores into quintiles (Table 3), age-adjusted geometric mean PSA significantly decreased across APRI, FIB-4 and NFS quintiles (p trend < 0.001). This trend was consistent after multivariable adjustment. Similar trends were also observed in the sensitivity analysis among males with BMI <30 kg/m^2 and among males without a diagnosis of diabetes or an elevated glycated hemoglobin, respectively (Supplement Table 1 and 2).

After stratifying by race, geometric mean PSA decreased more steeply with increasing fibrosis scores in non-Hispanic Whites than in non-Hispanic Blacks and in Mexican-Americans/other Hispanics (Figure 1.D-F). The trends among each race became more consistent after excluding the influential points (Supplement Figure 1. D-F). After dividing

fibrosis scores into quintiles, all three fibrosis scores were inversely associated with PSA concentration among non-Hispanic Whites and among Mexican-American/other Hispanics, whereas among non-Hispanic Blacks, fibrosis scores were not associated with PSA concentration (Table 4).

After restricting to men who reported a diagnosis of liver disease, geometric mean PSA decreased with increasing fibrosis scores in each racial/ethnic group (Figure 2). After dividing fibrosis scores into quintiles, geometric mean PSA decreased across quintiles of fibrosis scores overall and this pattern was observed in each racial/ethnic group; the trend was statistically significant after multivariable adjustment among non-Hispanic Whites and non-Hispanic Blacks (both p trends < 0.05; Supplement Table 3). In the sensitivity analyses we restricted to men with self-reported liver disease and/or viral hepatitis infection confirmed by serum test, there was a decreasing trend of geometric mean PSA with increasing fibrosis scores among the White men, but no association among Black men or Mexican American/other Hispanics (Supplement Table 4, Supplement Figure 2 and 3).

We also determined geometric mean PSA concentration within clinical categories of the fibrosis scores (Table 5). Regardless the score, males with abnormal scores suggestive of advanced fibrosis have significantly lower level of geometric mean serum PSA (range of difference: 0.15-0.21ng/mL). This pattern was also observed after multivariable adjustment, and was observed in each race/ethnicity across all three scores.

Liver fibrosis scores and elevated serum PSA concentration

Lastly, we examined the association between liver fibrosis scores and the odds of having elevated PSA, we selected 2 cut points which are often used as indication for prostate biopsy (Table 6). Overall, after multivariable adjustment, the odds ratios (OR) of elevated PSA for abnormal fibrosis score defined by APRI was 0.67 (95% CI: 0.39, 1.16) for PSA >2 ng/mL and 0.33 (95% CI: 0.11, 0.96) for PSA >4 ng/mL, for those with elevated FIB-4 the corresponding OR(95% CI) were 0.64(0.45, 0.92) and 0.67(0.44, 1.03), and for those with elevated NFS were 0.76(0.59, 0.98) and 0.71(0.50, 1.00) . After stratifying by race, similar trends were observed but did not reach statistical significance among each race/ethnicity group. For FIB-4 and NFS, men who had an abnormal score were less likely

to have a PSA >10 ng/mL, albeit 95% CIs were wide (data not shown); the analysis was too sparse for APRI.

To improve classification of abnormal and normal liver fibrosis scores, we classified the men by the number of the three abnormal APRI, FIB-4 and NFS fibrosis scores (0, 1, or 2 or 3 abnormal fibrosis scores). As shown in supplemental table 5, overall, compared with men with 0 abnormal scores, those with 1 abnormal and those with 2 or 3 abnormal fibrosis scores had a lower odds of PSA >2 ng/mL (OR: 0.83 and 0.59), PSA >4 ng/mL (OR: 0.80 and 0.55), and PSA > 10 ng/mL (OR: 0.76 and 0.45). After stratifying by race/ethnicity, the association between number of abnormal fibrosis scores and elevated PSA among each race/ethnicity was inverse as for overall, although was less strong among non-Hispanic Black and Mexican-American/other Hispanic men than that among the Whites.

DISCUSSION

In this US nationally representative study of men without a prostate cancer diagnosis, we found that men with higher liver fibrosis scores had lower serum PSA concentration. This association was consistent among individuals without obesity and also those without diabetes. Furthermore, the results were similar across race/ethnic groups. Given the increasing prevalence of liver fibrosis, as a result of the rising occurrence of nonalcoholic fatty liver disease, our findings have important implications for early detection of prostate cancer, especially in Black men who tend to have more aggressive prostate cancer.

To date, no consensus has been reached regarding the impact of liver function on PSA concentration. To our knowledge, our study is the first to examine this association among men aged older than 40 years in the overall US population, and the results are consistent with previous studies observing that serum PSA tended to be lower in men with cirrhosis than men without cirrhosis.[1,2,5,33,34] With respect to liver function, a study of 38,157 healthy Korean males also found that men with a higher serum concentration of the liver enzyme ALT had a lower PSA concentration.[6] Additionally, a small number of studies conducted in the US found that PSA concentration was lower among patients with liver diseases than in men with normal function, although these findings were based on fewer cases and were not statistically significant. [35-37]

Over the last 25 years, testing for elevated PSA has been widely used for the early detection of prostate cancer in the US.[7] More recently, uptake has decreased due to changing screening recommendations from the US Preventive Services Task Force (USPSTF) in 2012.[38-40] However, the early detection of prostate cancer by PSA testing coupled with appropriate treatment can reduce the risk of death for a subset of men with lethal type prostate cancer.[41] For men with liver fibrosis and consequent falsely lower PSA concentration could delay their detection and treatment of lethal type prostate cancer, possibly increasing risk of death from this cancer. Draft PSA-based prostate cancer screening guidelines released by the USPSTF in 2017 indicate that providers should discuss the benefits and risk of this test for each patient.[40] Whether liver disease should be a component of that discussion and also considered in the interpretation of the PSA results

remains to be determined, as does how reduced life expectancy due to liver disease affects the benefit to risk ratio for screening.

In this nationally representative study, we also found that the association between liver fibrosis score and PSA level across each of the US race/ethnic groups studied. Compared with White men, Black men have a significantly higher incidence of prostate cancer, are more likely to develop prostate cancer at younger ages, and are more likely to die of prostate cancer. [10] Although the racial disparities are not consistent across liver diseases (i.e. African American has higher risk of infectious hepatitis, while Mexican American has higher risk of NAFLD)[13,14], in our study population, the proportion of males with abnormal liver fibrosis score was higher among African American than among non-Hispanic Whites or Mexican Americans. Given the results of our study, men with presumed liver fibrosis were less likely to have PSA >4 ng/mL and would not be referred to prostate biopsy. Moreover, among patients with self-repoted liver condition, the PSA concentration among non-Hispanic Blacks tended to decrease faster with per unit increase of fibrosis score compared with males of other race groups. Therefore, African-American men may be more likely to have delayed detection of prostate cancer attributable to a higher prevalence of liver fibrosis and a higher risk of prostate cancer than their non-Hispanic White or Mexican American counterparts.

In our analysis restricted to people with diagnosed liver diseases, the association between liver fibrosis scores and PSA concentration was even stronger than that in the overall study population, especially among non-Hispanic Black and Mexican American/other Hispanic men; that is, patients with liver disease are even more likely to have reduced serum PSA concentration if they have-severe liver fibrosis. Whether men with liver disease and severe fibrosis would benefit from prostate cancer screening given the likelihood of reduced life expectancy is beyond the scope of this manuscript and future studies are needed to determine if this is the case.

The strengths of our study include that we used a nationally representative sample of men in the age range often targeted for the early detection of prostate cancer. Measurements of liver enzymes and PSA were not performed for clinical indication and the men were not enriched for liver disease. Instead, these measurements were performed-on all eligible men

as part of the NHANES protocol to understand the health and nutritional status of Americans. Thus, the findings are likely generalizable to the US men in these age ranges. Secondly, each biomarker was measured under the same protocol in the same laboratory. Moreover, this is the first and largest study to examine the association between liver fibrosis and PSA in different races/ethnicities.

One possible limitation of our study is that we used non-invasive indicators to define liver fibrosis, which may result in misclassification compared with imaging and the gold standard liver biopsy. We used three fibrosis scores that were primarily developed for different liver conditions but that have been validated in different populations. [23,28]Given that each is purported to measure liver fibrosis, we performed a sensitivity analysis in which cross-categorized the men with respect to all three of the scores. In doing so, we expected that men who truly had liver fibrosis would be more likely score high on two or three of these scores, while those who truly did not have liver fibrosis would be more likely to score low on all three of these scores. The results (i.e., lower PSA in those most likely to have liver fibrosis than in those unlikely to have liver fibrosis) when using the cross-classification categories were consistent with those when using the three scores separately.

Another limitation of the current study is that it was cross-sectional, and we are not able to evaluate how progression to fibrosis influences PSA concentration. We were not able to study the mechanism by which liver fibrosis influences the detectable level of PSA in circulation. We had initially hypothesized that liver fibrosis would be associated with higher serum PSA because the liver is the primary site for PSA metabolism and clearance.[4,42] However, we also recognized that men with liver cirrhosis have substantially lower testosterone levels,[43] and given that PSA is under androgenic regulation,[44] we alternatively hypothesized that men with fibrosis may have lower serum PSA due to their reduced testosterone level.

We cannot rule out that the inverse association that we observed between liver fibrosis scores and PSA is explained by men with abnormal liver function being less likely to develop prostate cancer, and thus have lower serum PSA levels. As prostate growth is dependent on androgens, levels of which can be influenced by hepatic function, liver disease may impact the risk of prostate cancer.[44,45] To address this alternative explanation

for our findings, a prospective study of men with and without liver disease followed for a decade or more for the development of clinically-detectable prostate cancer or for prostate cancer detected by biopsy performed irrespective of PSA level would be needed. Such a study is unlikely to be conducted in the future. Nevertheless, irrespective of the mechanism by which poor liver function may affect serum PSA and the development of prostate cancer (and associated PSA level), it may serve as a patient characteristic that could be considered in the discussion on PSA-based prostate cancer screening and possibly in the interpretation of the PSA value.

In conclusion, men with an abnormal liver fibrosis score may be less likely to have an elevated PSA. Lower PSA could results in a higher probability of delayed detection of prostate cancer, including disease with a lethal phenotype, including in Black men who are more likely to have aggressive prostate cancer and die of this cancer.

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APPENDIX

Table 1. Characteristics by Liver Fibrosis Scores Among Men 40 Years and Older, NHANES 2001-2010

	Overall	APRI		FIB-4		NFS	
		Normal	Abnormal[a]	Normal	Abnormal	Normal	Abnormal
Unweighted Participants	6,705	6,541	164	6,319	386	6,139	566
Mean age at survey, years (standard error)	55.1(0.2)	55.1(0.2)	54.5(0.9)	54.6(0.2)	68.3(0.8)	54.3(0.2)	68.8(0.5)
Race/ethnicity, % (95% Confidence Interval)							
White (non-Hispanic)	77.1 (74.5-79.7)	77.3 (74.7-79.9)	67.4 (57.4-77.4)	77.2 (74.6-79.7)	76.4 (71.0-81.9)	77.0 (74.2-79.5)	79.8 (75.4-83.6)
Black (non-Hispanic)	8.6 (7.3-9.8)	8.5 (7.2-9.7)	14.4 (8.6-20.1)	8.5 (7.3-9.7)	10.6 (7.3-13.8)	8.6 (7.4-9.9)	8.3 (6.2-11.0)
Mexican-American/Other Hispanic	9.6 (7.7-11.5)	9.5 (7.6-11.4)	12.5 (6.5-18.6)	9.7 (7.8-11.6)	7.1 (4.1-10.1)	9.8 (8.0-11.9)	6.6 (4.8-9.0)
Other	4.7 (3.8-5.6)	4.7 (3.7-5.6)	5.7 (0.7-10.7)	4.7 (3.7-5.6)	5.9 (2.7-9.1)	4.7 (3.8-5.7)	5.4 (3.5-8.1)
Education level, % (95% Confidence Interval)							
Less than 9th grade	7.4 (6.5-8.2)	7.3 (6.4-8.1)	11.0 (5.9-16.2)	7.1 (6.3-7.9)	14.3 (10.7-17.9)	6.9 (6.1-7.8)	15.0 (11.3-19.6)
9-11th grade (includes 12th grade with no diploma)	10.2 (9.2-11.3)	10.1 (9.0-11.1)	18.5 (10.3-26.7)	10.1 (9.0-11.1)	15 (10.1-19.9)	10.1 (9.1-11.3)	11.6 (9.2-14.6)
High school graduate/GED or equivalent	25.2 (23.8-26.6)	25.0 (23.6-26.4)	33.1 (24.7-41.6)	25.2 (23.8-26.6)	24.6 (18.6-30.6)	25.5 (23.9-26.6)	24.8 (21.0-29.0)
Some college or associates degree	27.4 (26.0-28.9)	27.5 (26.1-29.0)	22.4 (14.4-30.4)	27.6 (26.2-29.1)	21.8 (16.0-27.7)	27.4 (26.0-29.0)	27.3 (21.5-34.1)
College graduate or above	29.8 (27.6-32.0)	30.1 (27.9-32.3)	14.9 (7.2-22.6)	30.0 (27.7-32.2)	24.3 (18.1-30.5)	30.3 (28.0-32.6)	21.3 (16.9-26.4)
Drinking status, % (95% Confidence Interval)							
Non-drinker or non-heavy drinker	91.2 (90.3-92.1)	91.6 (90.8-92.5)	70.2 (62.3-78.1)	91.4 (90.5-92.3)	85.7 (81.4-90.1)	91.0 (90.0-91.9)	94.2 (91.6-96.0)
Heavy drinker	8.8 (7.9-9.7)	8.4 (7.5-9.2)	29.8 (21.9-37.7)	8.6 (7.7-9.5)	14.3 (9.9-18.6)	9.0 (8.1-10.0)	5.8 (4.0-8.4)

Smoking history, % (95% Confidence Interval)							
Never	41.7 (39.7-43.6)	42.1 (40.1-44.1)	23.9 (14.6-33.3)	41.9 (39.9-43.9)	35.2 (29.7-40.7)	42.1 (40.0-44.1)	35.3 (31.1-39.8)
Ever	58.3 (56.4-60.3)	57.9 (55.9-59.9)	76.1 (66.7-85.4)	58.1 (56.1-60.1)	64.8 (59.3-70.3)	57.9 (55.9-60.0)	64.7 (60.2-68.9)
BMI category, % (95% Confidence Interval)							
Normal/overweight (<30 kg/m^2)	65.4 (63.7-67.2)	65.5 (63.8-67.3)	62.0 (52.9-71.1)	65.3 (63.5-67.1)	69.1 (63-75.2)	67.4 (65.6-69.1)	32.5 (28.8-36.4)
Obese (≥30 kg/m^2)	34.6 (32.8-36.3)	34.5 (32.7-36.2)	38.0 (28.9-47.1)	34.7 (32.9-36.5)	30.9 (24.8-37.0)	32.6 (30.9-34.4)	67.5 (63.6-71.2)
Diabetes status, % (95% Confidence Interval)							
No diabetes	63.5 (62.1-65.0)	63.6 (62.2-65.0)	61.9 (52.8-71.0)	64.0 (62.5-65.4)	51.7 (44-59.5)	65.9 (64.4-67.3)	24.5 (20.6-28.9)
At risk for diabetes	22.5 (21.4-23.7)	22.6 (21.4-23.8)	17.5 (9.6-25.3)	22.4 (21.2-23.7)	24.8 (19.2-30.4)	22.3 (21.1-23.6)	25.4 (21.2-30.1)
Controlled diabetes	5.8 (5.0-6.6)	5.7 (4.9-6.6)	7.7 (2.9-12.5)	5.5 (4.7-6.3)	12.5 (7.0-18.0)	4.5 (3.8-5.4)	26.7 (22.1-32.0)
Uncontrolled diabetes	8.2 (7.3-9.1)	8.1 (7.2-9.0)	12.9 (6.1-19.7)	8.1 (7.2-9.0)	10.9 (7.4-14.4)	7.3 (6.4-8.2)	23.4 (19.1-28.3)
Self-reported liver disease, % (95% Confidence Interval)							
Never	95.2 (94.5-95.8)	95.6 (95.0-96.2)	75.7 (64.7-84.1)	95.6 (94.9-96.2)	85.1 (78.8-89.8)	95.4 (94.6-96.0)	92.4 (88.4-95.1)
Ever	4.8 (4.2-5.5)	4.4 (3.8-5.0)	24.3 (15.9-35.3)	4.4 (3.8-5.1)	14.9 (10.2-21.2)	4.6 (4.0-5.4)	7.6 (4.9-11.6)
HCV status, % (95% Confidence Interval)							
HCV negative	96.7 (96.0-97.3)	97.4 (96.7-97.9)	65.3 (55.6-74.0)	97.1 (96.4-97.6)	86.2 (80.4-90.4)	96.7 (96.0-97.3)	96.1 (93.4-97.7)
HCV infected	3.3 (2.7-4.0)	2.6 (2.1-3.3)	34.7 (26.0-44.4)	2.9 (2.4-3.6)	13.8 (9.6-19.6)	3.3 (2.7-4.0)	4.0 (2.3-6.6)
HBV status, % (95% Confidence Interval)							
HBV negative	92.2 (91.2-93.0)	92.4 (91.5-93.3)	79.2 (70.0-86.1)	92.4 (91.4-93.3)	85.6 (79.8-89.9)	92.3 (91.3-93.2)	90.1 (86.6-92.7)
Current or previous HBV infected	7.8	7.6	20.8	7.6	14.4	7.7	9.9

	(7.0-8.8)	(6.7-8.5)	(13.9-30.0)	(6.7-8.6)	(10.1-20.2)	(6.8-8.7)	(7.3-13.4)
Chronic HBV infected	0.5 (0.3-0.7)	0.5 (0.3-0.7)	1.2 (3.5-4.0)	0.5 (0.3-0.7)	0.5 (0.2-1.7)	0.5 (0.3-0.7)	0.3 (0.1-1.2)

[a] Cutpoint for abnormal liver fibrosis score equates to advanced fibrosis (APRI>1, FIB-4 >2.67 and NFS>0.676.)

Table 2. Characteristics by PSA Level Among Men 40 Years and Older, NHANES 2001-2010

	PSA serum concentration (ng/mL)				
	<1	**1 to <2**	**2 to <4**	**4 to <10**	**≥10**
Unweighted Participants	3,338	1,809	961	482	115
Mean age at survey, years (standard error)	52.1(0.2)	55.7(0.3)	61.5(0.4)	66.8(0.6)	69.0(1.9)
Race/ethnicity, % (95% Confidence Interval)					
White (non-Hispanic)	76.9 (74.3-79.5)	76.0 (72.3-79.7)	79.7 (76.1-83.3)	80.2 (76.2-84.3)	69.3 (59.0-79.5)
Black (non-Hispanic)	8.2 (6.9-9.5)	8.8 (7.3-10.3)	8.8 (6.7-10.9)	9.0 (6.5-11.6)	16.5 (8.7-24.4)
Mexican-American/Other Hispanic	10.0 (8.0-12.0)	10.0 (7.4-12.5)	8.6 (6.2-11.0)	6.0 (4.4-7.7)	10.9 (3.7-18.1)
Other	4.8 (3.7-5.9)	5.2 (3.5-6.9)	2.9 (1.2-4.6)	4.7 (2.1-7.4)	3.3 (1.0-7.7)
Education level, % (95% Confidence Interval)					
Less than 9th grade	6.8 (5.7-7.9)	6.5 (5.3-7.6)	9.4 (7.8-11)	10.2 (7.3-13.1)	14.8 (7.5-22.1)
9-11th grade (includes 12th grade with no diploma)	10.2 (8.9-11.5)	9.9 (8.2-11.6)	9.8 (7.9-11.7)	11.0 (7.5-14.6)	17.7 (8.1-27.3)
High school graduate/GED or equivalent	25.0 (22.9-27)	25.8 (22.9-28.6)	26.8 (23.1-30.5)	23.4 (18.9-27.9)	21.7 (10.8-32.6)
Some college or associates degree	28.5 (26.3-30.6)	27.4 (24.9-30)	26.5 (22.3-30.7)	19.6 (14.8-24.4)	25.9 (13.8-38.0)
College graduate or above	29.6 (26.9-32.3)	30.4 (27.0-33.8)	27.5 (23.2-31.7)	35.7 (29.4-42.1)	19.9 (10.3-29.5)
Drinking status, % (95% Confidence Interval)					
Non-drinker or non-heavy drinker	91.4 (90.3-92.6)	89.1 (87.2-91.1)	93.4 (91.3-95.5)	91.0 (87.5-94.5)	96.8 (93.9-99.7)
Heavy drinker	8.6 (7.4-9.7)	10.9 (8.9-12.8)	6.6 (4.5-8.7)	9.0 (5.5-12.5)	3.2 (0.3-6.1)
Smoking history, % (95% Confidence Interval)					
Never	42.4 (40.3-44.5)	41.6 (38.4-44.8)	37.6 (33.0-42.2)	43.4 (37.4-49.4)	46.0 (32.9-59.1)
Ever	57.6 (55.5-59.7)	58.4 (55.2-61.6)	62.4 (57.8-67.0)	56.6 (50.6-62.6)	54.0 (40.9-67.1)
BMI category, % (95% Confidence Interval)					

Normal/overweight (<30 kg/m^2)	62.7 (60.4-64.9)	69.0 (66.1-72.0)	65.5 (61.4-69.7)	74.0 (69.4-78.6)	79.5 (69.3-89.7)
Obese (≥30 kg/m^2)	37.3 (35.1-39.6)	31.0 (28.0-33.9)	34.5 (30.3-38.6)	26.0 (21.4-30.6)	20.5 (10.3-30.7)
Diabetes status, % (95% Confidence Interval)					
No diabetes	64.5 (62.4-66.6)	65.3 (62.7-68.0)	57.7 (53.5-62.0)	59.6 (54.5-64.7)	56.3 (44.4-68.1)
At risk for diabetes	21.7 (19.8-23.5)	22.0 (19.9-24.2)	25.8 (22.3-29.3)	25.5 (21.4-29.5)	28.6 (18.3-38.8)
Controlled diabetes	5.4 (4.3-6.6)	5.7 (4.3-7.1)	7.2 (5.3-9.1)	6.2 (3.6-8.7)	4.0 (0.4-7.6)
Uncontrolled diabetes	8.4 (7.3-9.6)	7.0 (5.6-8.4)	9.2 (7.5-11.0)	8.8 (5.5-12)	11.2 (5.1-17.3)
Self-reported liver disease, % (95% Confidence Interval)					
Never	94.6 (93.6-95.5)	95.5 (93.9-96.7)	96.5 (94.7-97.6)	96.6 (93.9-98.1)	98.1 (92.1-99.6)
Ever	5.4 (4.5-6.4)	4.5 (3.3-6.1)	3.5 (2.4-5.3)	3.4 (1.9-6.1)	1.9 (0.4-7.9)
HCV status, % (95% Confidence Interval)					
HCV negative	96.0 (95.0-96.9)	96.8 (95.5-97.8)	98.6 (97.4-99.3)	98.1 (95.2-99.2)	100.0 (100.0-100.0)
HCV infected	4.0 (3.1-5.0)	3.2 (2.2-4.5)	1.4 (0.7-2.6)	1.9 (0.8-4.8)	--
HBV status, % (95% Confidence Interval)					
HBV negative	92.8 (91.6-93.8)	91.4 (89.2-93.1)	93.1 (90.9-94.8)	88.0 (83.8-91.2)	86.9 (76.6-93.1)
Current or previous HBV infected	7.2 (91.6-93.8)	8.6 (6.9-10.8)	6.9 (5.2-9.1)	12.0 (8.8-16.2)	13.1 (6.9-23.4)
Chronic HBV infected	0.4 (0.2-0.8)	0.6 (0.3-1.3)	0.5 (0.2-1.8)	0.1 (0.0-0.6)	--

Table 3. Geometric Mean Serum PSA Concentration (ng/mL) and 95% Confidence Intervals by Quintile of Fibrosis Scores Among Men 40 Years and Older, NHANES 2001-2010

	APRI					
	Q1 (<0.24)	**Q2 (0.24 to <0.29)**	**Q3 (0.29 to <0.35)**	**Q4 (0.35 to <0.44)**	**Q5 (≥0.44)**	**Per 1 unit increase in fibrosis score (p trend)**
Model 1[a]	1.03 (0.98,1.09)	0.96 (0.91,1.02)	0.94 (0.89,0.99)	0.97 (0.93,1.01)	0.89 (0.84,0.95)	-0.36 (<0.001)
Model 2[b]	1.04 (0.99,1.10)	0.96 (0.91,1.02)	0.93 (0.89,0.98)	0.97 (0.93,1.01)	0.89 (0.84,0.95)	-0.38 (<0.001)
	FIB4					
	Q1 (<0.79)	**Q2 (0.79 to <0.99)**	**Q3 (0.99 to <1.23)**	**Q4 (1.23 to <1.62)**	**Q5 (≥1.62)**	**Per 1 unit increase in fibrosis score (p trend)**
Model 1	1.03 (0.97,1.08)	0.96 (0.92,1.01)	0.97 (0.91,1.03)	0.94 (0.89,0.99)	0.90 (0.84,0.96)	-0.09 (0.007)
Model 2	1.04 (0.99,1.10)	0.97 (0.93,1.02)	0.97 (0.92,1.03)	0.94 (0.89,0.99)	0.88 (0.83,0.95)	-0.11 (0.001)
	NFS					
	Q1 (<0.17)	**Q2 (0.17 to <0.89)**	**Q3 (0.89 to <1.58)**	**Q4 (1.58 to <2.42)**	**Q5 (≥2.42)**	**Per 1 unit increase in fibrosis score (p trend)**
Model 1	1.05 (1.00,1.11)	0.99 (0.94,1.04)	1.01 (0.96,1.05)	0.92 (0.86,0.98)	0.84 (0.78,0.91)	-0.06 (<0.001)
Model 2	1.02 (0.96,1.08)	0.96 (0.92,1.01)	1.00 (0.95,1.04)	0.93 (0.87,0.99)	0.89 (0.82,0.96)	-0.04 (0.017)

[a] Model 1 adjusted for age and race;

[b] Model 2 adjusted for the age, race, BMI category, diabetes status, alcohol drinking status and smoking status.

Table 4. Association Between Fibrosis Score and Natural Logarithm Transformed Serum PSA Concentration (ng/mL) by Race/Ethnicity Among Men 40 Years and Older, NHANES 2001-2010

	White (non-Hispanic)		Black (non-Hispanic)		Mexican-American/Other Hispanic	
	APRI					
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1[a]	-0.40	<0.001	-0.03	0.89	-0.32	0.073
Model 2[b]	-0.41	<0.001	-0.01	0.66	-0.34	0.065
	FIB4					
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.09	0.039	0.00	0.96	-0.14	0.020
Model 2	-0.11	0.012	-0.03	0.66	-0.15	0.016
	NFS					
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.06	<0.001	-0.01	0.68	-0.04	0.083
Model 2	-0.04	0.051	0.01	0.82	-0.03	0.37

[a] Model 1 adjusted for age and race;
[b] Model 2 adjusted for the age, race, BMI category, diabetes status, alcohol drinking status and smoking status.

Table 5. Geometric Mean Serum PSA Concentration (ng/mL) and 95% Confidence Intervals by Abnormal versus Normal Fibrosis Scores Overall and By Race/Ethnicity Among Men 40 Years and Older, NHANES 2001-2010

	Overall		White (non-Hispanic)		Black (non-Hispanic)		Mexican-American /Other Hispanic	
	APRI							
	Normal	**Abnormal[c]**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**
Model 1[a]	**0.96**	**0.75**	**0.97**	**0.69**	1.00	0.86	0.95	0.89
	(0.94,0.99)	**(0.64,0.88)**	**(0.94,1.00)**	**(0.55,0.86)**	(0.95,1.06)	(0.66,1.12)	(0.89,1.01)	(0.72,1.09)
Model 2[b]	**0.96**	**0.76**	**0.97**	**0.71**	1.00	0.82	0.95	0.9
	(0.94,0.99)	**(0.64,0.89)**	**(0.94,1.00)**	**(0.57,0.89)**	(0.95,1.07)	(0.63,1.07)	(0.89,1.01)	(0.72,1.13)
	FIB4							
	Normal	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**
Model 1	**0.96**	**0.81**	**0.97**	**0.79**	1.00	0.92	0.95	0.88
	(0.94,0.99)	**(0.70,0.93)**	**(0.94,1.00)**	**(0.66,0.95)**	(0.94,1.06)	(0.72,1.18)	(0.89,1.01)	(0.67,1.15)
Model 2	**0.96**	**0.80**	**0.97**	**0.79**	1.00	0.89	0.95	0.88
	(0.94,0.99)	**(0.70,0.93)**	**(0.94,1.00)**	**(0.66,0.95)**	(0.95,1.06)	(0.69,1.13)	(0.89,1.01)	(0.66,1.17)
	NFS							
	Normal	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**
Model 1	**0.97**	**0.77**	**0.97**	**0.78**	1.00	0.98	0.95	0.82
	(0.95,1.00)	**(0.71,0.84)**	**(0.94,1.00)**	**(0.71,0.86)**	(0.94,1.06)	(0.79,1.22)	(0.89,1.01)	(0.66,1.01)
Model 2	**0.97**	**0.83**	**0.97**	**0.85**	1.00	1.02	0.95	0.84
	(0.94,0.99)	**(0.77,0.90)**	**(0.94,1.00)**	**(0.77,0.94)**	(0.94,1.06)	(0.81,1.29)	(0.89,1.01)	(0.69,1.04)

[a] Model 1 adjusted for age and race, numbers with bold font implies $p<0.05$;

[b] Model 2 adjusted for the age, race, BMI category, diabetes status, alcohol drinking status and smoking status;

[c] Cutpoint for abnormal liver function equates to advanced fibrosis (APRI>1, FIB-4 >2.67 and NFS>0.676.)

Table 6. Association between Abnormal Fibrosis Score and Elevated Serum PSA Concentration Overall and by Race/Ethnicity Among Men 40 Years and Older, NHANES 2001-2010

PSA concentration (ng/mL)	Odds Ratio (95% Confidence Interval) [a]			
	Overall	White (non-Hispanic)	Black (non-Hispanic)	Mexican-American/ Other Hispanic
			APRI	
>2	0.67 (0.39,1.16)	0.58 (0.28,1.22)	0.99 (0.35,2.85)	0.83 (0.30,2.33)
>4	0.33 (0.11,0.96)	0.26 (0.06,1.21)	0.19 (0.02,1.70)	0.28 (0.03,2.22)
			FIB4	
>2	0.64 (0.45,0.92)	0.59 (0.38,0.92)	1.24 (0.61,2.53)	0.95 (0.42,2.15)
>4	0.67 (0.44,1.03)	0.69 (0.42,1.12)	0.59 (0.27,1.28)	0.66 (0.24,1.82)
			NFS	
>2	0.76 (0.59,0.98)	0.75 (0.56,1.01)	0.88 (0.50,1.57)	1.08 (0.59,1.97)
>4	0.71 (0.50,1.00)	0.70 (0.47,1.04)	0.55 (0.24,1.27)	0.83 (0.34,2.02)

[a] Adjusted for the age, BMI category, diabetes status, alcohol drinking status and smoking status.

Supplement Table 1. Association Between Fibrosis Score and Natural Logarithm Transformed Serum PSA Concentration (ng/mL) by Race/Ethnicity Among Men 40 Years and Older and With BMI <30 kg/m^2, NHANES 2001-2010 (unweighted N = 4,458)

	Overall		White (non-Hispanic)		Black (non-Hispanic)		Mexican-American/Other Hispanic	
	APRI							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1[a]	-0.24	0.051	-0.30	0.047	-0.02	0.93	-0.08	0.72
Model 2[b]	-0.28	0.030	-0.34	0.030	-0.09	0.75	-0.09	0.69
	FIB4							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.08	0.060	-0.09	0.096	0.04	0.63	-0.10	0.19
Model 2	-0.09	0.048	-0.10	0.081	0.02	0.84	-0.11	0.14
	NFS							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.05	0.022	-0.05	0.053	0.01	0.87	-0.04	0.13
Model 2	-0.04	0.084	-0.04	0.16	0.02	0.67	-0.03	0.29

[a] Model 1 adjusted for age and race;

[b] Model 2 adjusted for the age, race, diabetes status, alcohol drinking status and smoking status.

Supplement Table 2. Association Between Fibrosis Score and Natural Logarithm Transformed Serum PSA Concentration (ng/mL) by Race/Ethnicity Among Men 40 Years and Older and Without a Diagnosis of Diabetes or an Elevated Glycated Hemoglobin, NHANES 2001-2010 (unweighted N = 3,656)

	Overall		White (non-Hispanic)		Black (non-Hispanic)		Mexican-American/Other Hispanic	
	APRI							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1[a]	-0.27	0.017	-0.28	0.047	0.01	0.97	-0.44	0.091
Model 2[b]	-0.30	0.012	-0.32	0.029	-0.03	0.91	-0.46	0.077
	FIB4							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.08	0.050	-0.07	0.15	0.00	0.97	-0.2	0.012
Model 2	-0.09	0.026	-0.09	0.083	-0.02	0.80	-0.21	0.020
	NFS							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.03	0.13	-0.02	0.24	0.01	0.68	-0.02	0.66
Model 2	-0.03	0.18	-0.02	0.29	0.02	0.65	-0.04	0.43

[a] Model 1 adjusted for age and race;
[b] Model 2 adjusted for the age, race, BMI category, , alcohol drinking status and smoking status.

Supplement Table 3. Association Between Fibrosis Score and Natural Logarithm Transformed Serum PSA Concentration (ng/mL) by Race/Ethnicity Among Men 40 Years and Older and With Self-reported Liver Disease, NHANES 2001-2010 (unweighted N = 288)

	Overall		White (non-Hispanic)		Black (non-Hispanic)		Mexican-American/Other Hispanic	
	APRI							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1[a]	-1.03	0.008	-1.14	0.019	-1.27	0.23	-0.23	0.85
Model 2[b]	-1.09	0.002	-1.14	0.008	-2.46	0.027	-0.24	0.79
	FIB4							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.36	0.009	-0.32	0.058	-0.25	0.51	-0.30	0.15
Model 2	-0.41	0.003	-0.35	0.031	-0.80	0.042	-0.19	0.44
	NFS							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.17	<0.001	-0.16	0.001	-0.42	0.016	-0.24	0.019
Model 2	-0.15	<0.001	-0.13	0.007	-0.24	0.019	-0.15	0.16

[a] Model 1 adjusted for age and race;
[b] Model 2 adjusted for the age, race, BMI category, diabetes status, alcohol drinking status and smoking status.

Supplement Table 4. Association Between Fibrosis Score and Natural Logarithm Transformed Serum PSA Concentration (ng/mL) by Race/Ethnicity Among Men 40 Years and Older and With Self-reported Liver Disease and/or Current or Previous Viral Hepatitis [a], NHANES 2001-2010 (unweighted N = 935)

	Overall		White (non-Hispanic)		Black (non-Hispanic)		Mexican-American/Other Hispanic	
	APRI							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1[b]	-0.24	0.051	-0.30	0.047	-0.02	0.93	-0.08	0.72
Model 2[c]	-0.28	0.030	-0.34	0.030	-0.09	0.75	-0.09	0.69
	FIB4							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.77	0.002	-0.95	-0.004	0.01	0.97	-0.45	0.52
Model 2	-0.84	0.001	-1.00	<0.001	-0.14	0.73	-0.31	0.64
	NFS							
	Per 1 unit increase in fibrosis score	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**	**Per 1 unit increase in fibrosis score**	**p trend**
Model 1	-0.16	<0.001	-0.18	<0.001	-0.04	0.46	-0.17	0.021
Model 2	-0.13	<0.001	-0.14	0.001	-0.01	0.86	-0.11	0.20

[a] Current or previous viral Hepatitis was defined as anti-HCV positive or anti-HBc positive;
[b] Model 1 adjusted for age and race;
[c] Model 2 adjusted for the age, race, BMI category, diabetes status, alcohol drinking status and smoking status.

Supplement Table 5. Association between Joint Indicators of Abnormal APRI, FIB4 and NFS Scores and Elevated Serum PSA Concentration Overall and by Race/Ethnicity Among Men 40 Years and Older, NHANES 2001-2010

PSA concentration	Odds Ratio (95% Confidence Interval) [a] for number of Abnormal Liver Fibrosis Scores											
	Overall			White (non-Hispanic)			Black (non-Hispanic)			Mexican-American/Other Hispanic		
	0[b]	1[c]	2[d]	0	1	2	0	1	2	0	1	2
>2	1 [reference]	0.83 (0.65,1.07)	0.59 (0.39,0.89)	1 [reference]	0.82 (0.60,1.12)	0.53 (0.32,0.87)	1 [reference]	1.53 (0.91,2.59)	0.93 (0.39,2.27)	1 [reference]	0.75 (0.47,1.20)	0.1.11 (0.39,3.13)
>4	1 [reference]	0.80 (0.57,1.12)	0.55 (0.33,0.91)	1 [reference]	0.82 (0.55,1.23)	0.53 (0.30,0.95)	1 [reference]	0.81 (0.35,1.88)	0.37 (0.12,1.12)	1 [reference]	0.75 (0.33,1.70)	0.68 (0.23,2.06)
>10	1 [reference]	0.76 (0.42,1.36)	0.45 (0.43,1.36)	1 [reference]	0.78 (0.40,1.53)	0.50 (0.13,1.86)	1 [reference]	0.85 (0.21,3.51)	0.20 (0.02,1.72)	1 [reference]	0.11 (0.01,0.99)	1.67 (0.39,7.23)

[a] Adjusted for the age, BMI category, diabetes status, alcohol drinking status and smoking status;
[b] 0: without any abnormal fibrosis score;
[c] 1: has only one abnormal fibrosis score;
[d] 2: has two or three abnormal fibrosis scores.

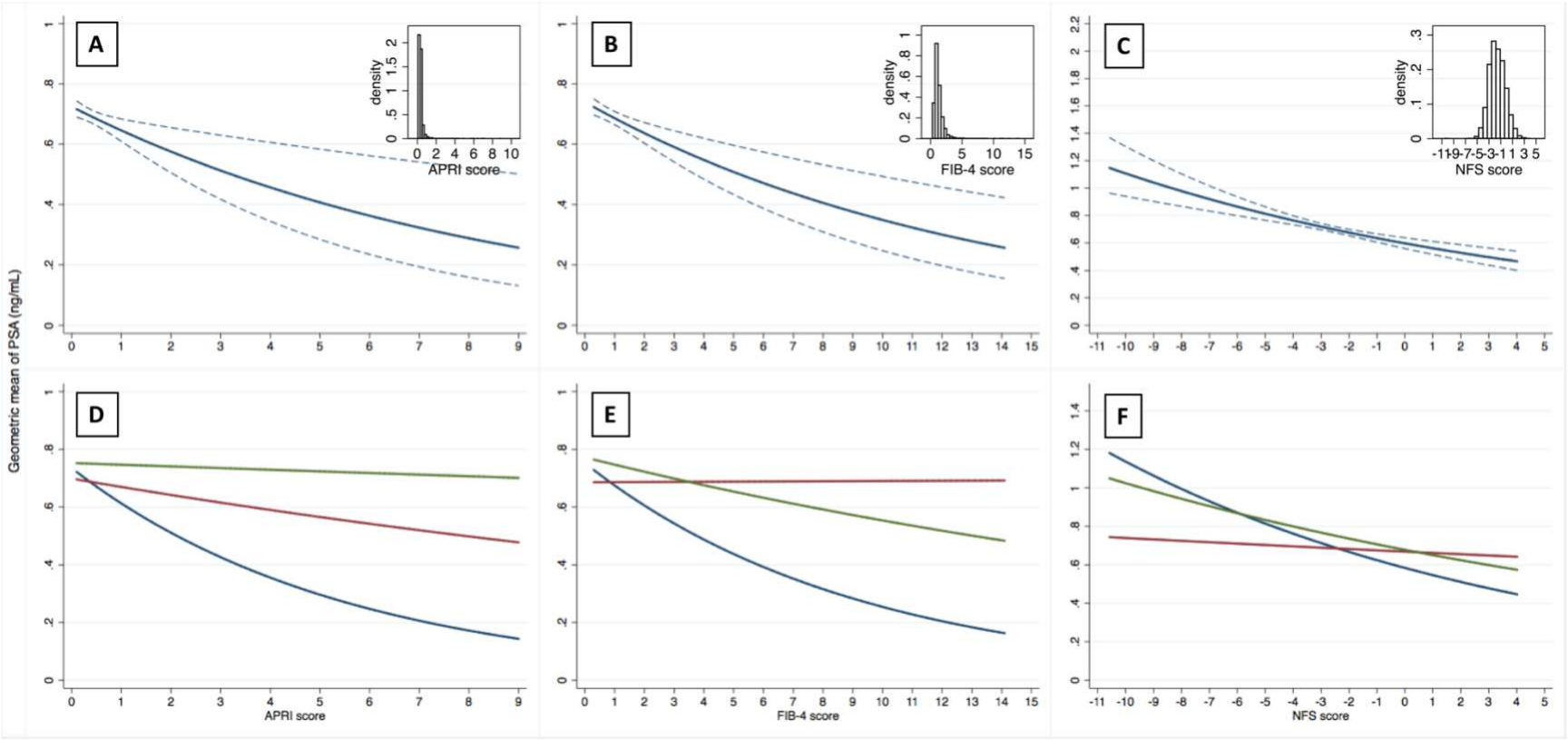


Figure 1. Association between Fibrosis Scores and Geometric Mean PSA Serum Concentration (ng/mL) Overall (Panel A, B, C) and By Race (Panel D, E, F) Among Men 40 Years and Older, NHANES 2001-2010

In the panel A, B and C, the solid line indicates the estimated geometric mean of PSA, while the dash line indicates the 95% Confidence Interval of the estimated geometric mean of PSA. The histogram at the upper right corner of each panel displays the density distribution of APRI, FIB-4, and NFS score, respectively. In the panel D, E and F, the blue line indicates the estimated geometric mean of PSA among non-Hispanic Whites, the red line indicates non-Hispanic Blacks, and the green line indicates Mexican American/other Hispanics. The x-axis ranges represent the true ranges of fibrosis scores among the analyzed population.

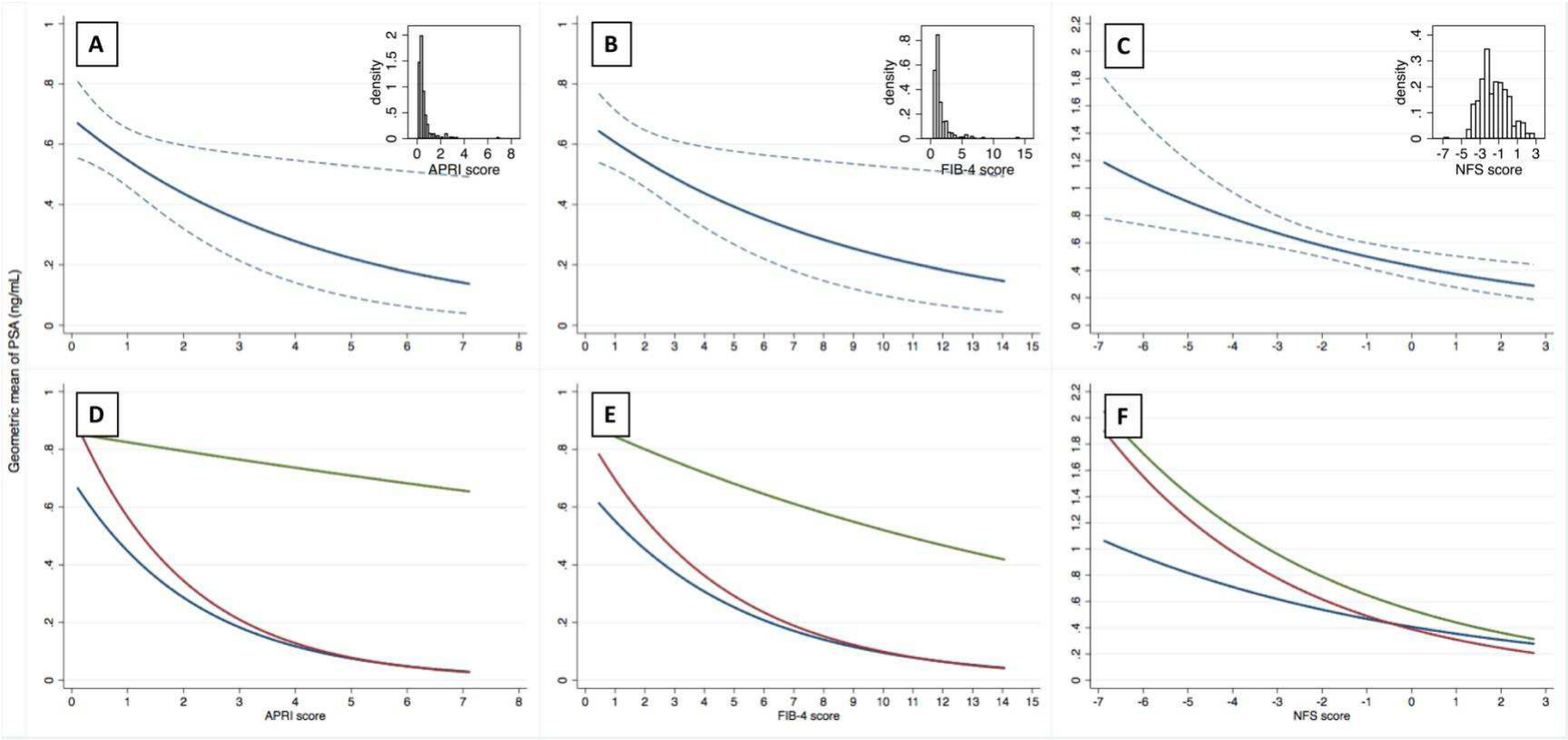
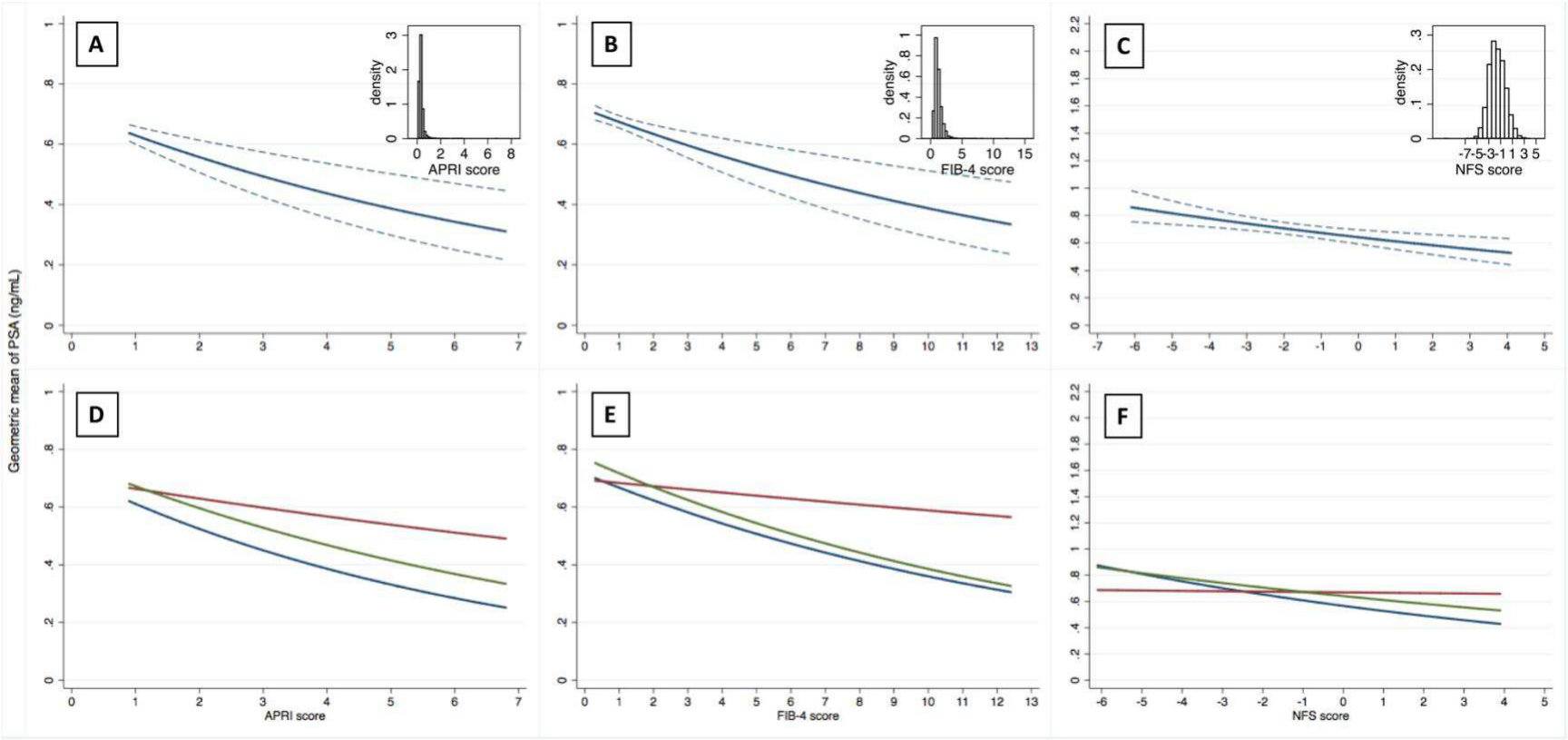


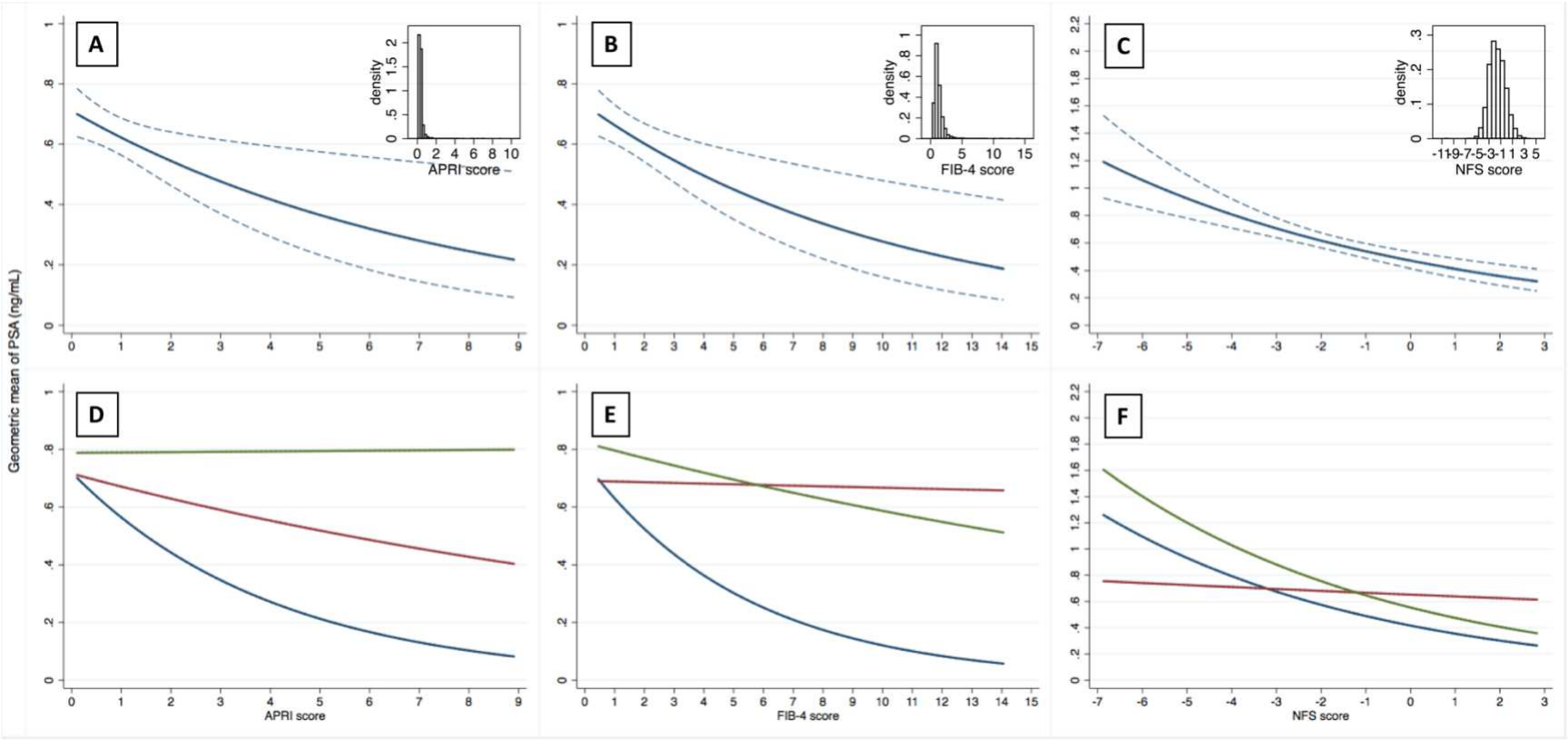
Figure 2. Association between Fibrosis Scores and Geometric Mean PSA Serum Concentration (ng/mL) Overall (Panel A, B, C) and By Race (Panel D, E, F) Among Men 40 Years and Older and With Self-reported Liver Disease, NHANES 2001-2010

In the panel A, B and C, the solid line indicates the estimated geometric mean of PSA, while the dash line indicates the 95% Confidence Interval of the estimated geometric mean of PSA. The histogram at the upper right corner of each panel displays the density distribution of APRI, FIB-4, and NFS score, respectively. In the panel D, E and F, the blue line indicates the estimated geometric mean of PSA among non-Hispanic Whites, the red line indicates non-Hispanic Blacks, and the green line indicates Mexican American/other Hispanics. The x-axis ranges represent the true ranges of fibrosis scores among the analyzed population.



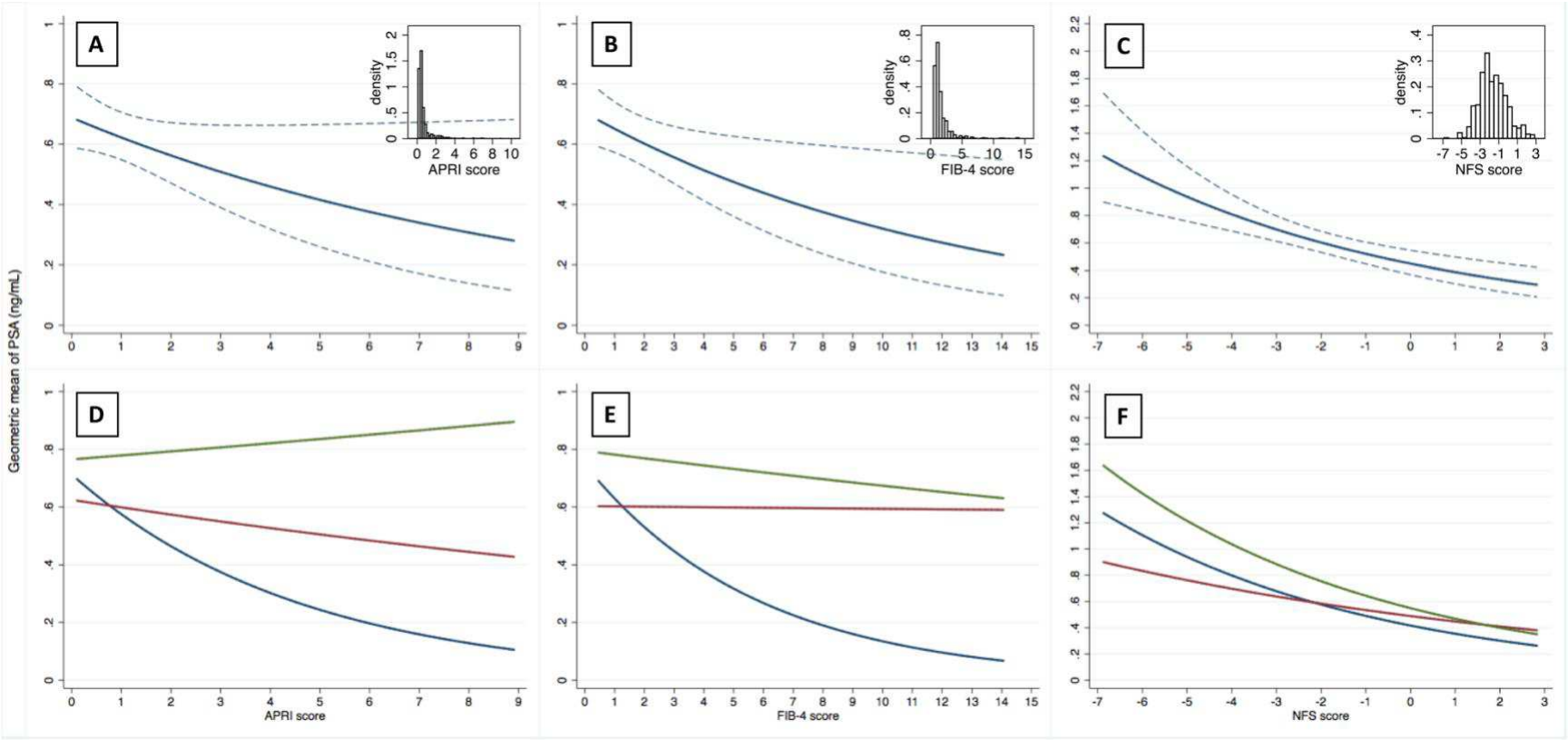
Supplement Figure 1. Association between Fibrosis Scores and Geometric Mean PSA Serum Concentration (ng/mL) Overall (Panel A, B, C) and By Race (Panel D, E, F) Among Men 40 Years and Older after Excluding Influential Points, NHANES 2001-2010

In the panel A, B and C, the solid line indicates the estimated geometric mean of PSA, while the dash line indicates the 95% Confidence Interval of the estimated geometric mean of PSA. The histogram at the upper right corner of each panel displays the density distribution of APRI, FIB-4, and NFS score, respectively. In the panel D, E and F, the blue line indicates the estimated geometric mean of PSA among non-Hispanic Whites, the red line indicates non-Hispanic Blacks, and the green line indicates Mexican American/other Hispanics. The x-axis ranges represent the true ranges of fibrosis scores among the analyzed population.



Supplement Figure 2. Association between Fibrosis Scores and Geometric Mean PSA Serum Concentration (ng/mL) Overall (Panel A, B, C) and By Race (Panel D, E, F) Among Men 40 Years and Older and With Self-reported Liver Disease and/or Current or Previous Viral Hepatitis, NHANES 2001-2010

In the panel A, B and C, the solid line indicates the estimated geometric mean of PSA, while the dash line indicates the 95% Confidence Interval of the estimated geometric mean of PSA. The histogram at the upper right corner of each panel displays the density distribution of APRI, FIB-4, and NFS score, respectively. In the panel D, E and F, the blue line indicates the estimated geometric mean of PSA among non-Hispanic Whites, the red line indicates non-Hispanic Blacks, and the green line indicates Mexican American/other Hispanics. The x-axis ranges represent the true ranges of fibrosis scores among the analyzed population. Current or previous viral hepatitis was defined as anti-HCV positive or anti-HBc positive.



Supplement Figure 3. Association between Fibrosis Scores and Geometric Mean PSA Serum Concentration (ng/mL) Overall (Panel A, B, C) and By Race (Panel D, E, F) Among Men 40 Years and Older and With Self-reported Liver Disease and/or Chronic Viral Hepatitis, NHANES 2001-2010
In the panel A, B and C, the solid line indicates the estimated geometric mean of PSA, while the dash line indicates the 95% Confidence Interval of the estimated geometric mean of PSA. The histogram at the upper right corner of each panel displays the density distribution of APRI, FIB-4, and NFS score, respectively. In the panel D, E and F, the blue line indicates the estimated geometric mean of PSA among non-Hispanic Whites, the red line indicates non-Hispanic Blacks, and the green line indicates Mexican American/other Hispanics. The x-axis ranges represent the true ranges of fibrosis scores among the analyzed population. Chronic viral hepatitis was defined as anti-HCV positive or HBsAg positive.

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EDUCATION

Master of Science (ScM) in Epidemiology **2016 – 2018**

Johns Hopkins Bloomberg School of Public Health – Baltimore, MD

Concentration: Cancer Epidemiology (Advisor: Elizabeth Platz)

- Certificate in Pharmacoepidemiology & Drug Safety
- Cumulative GPA: 4.0/4.0

Bachelor's Degree in Preventive Medicine (M.B.B.S) **2011 – 2016**

Peking University, School of Public Health – Beijing, CHINA

Certificate of Global Health **Aug-Dec 2015**

Duke University – Durham, NC

PUBLIC HEALTH RESEARCH EXPERIENCE

Child Health Epidemiology Reference Group (CHERG) **Dec 2017-Jun 2018**

Research Assistant

- Working on the Maternal and Child Epidemiology Estimation (MCEE) project, responsible for updating a global database of child mortality data to provide estimates of causes of death in children, as well as in expanding this work to cover adolescent causes of death.
- Performed systematic review on more than 23,000 articles, extracted and synthesis those data.
- Data management and data analysis

Epilepsy Center, Johns Hopkins Hospital **Jun-Sep 2017**

Data analyst

- Conducted risk factor analysis for eclampsia using weighted data representative for the US population.

Gastroenterology Department, Johns Hopkins Hospital **2016 – 2017**

Research Assistant

- Extracted liver cancer patients' indexes from hospital records system, developed dataset for longitudinal data.
- Used cox model investigating circulating tumor cells and circulating tumor DNA as prognostic biomarkers for liver cancer recurrence in patients who have liver transplantation

Department of Child, Adolescent and Women's Health, Peking University **2013 – 2016**

Research Assistant

- Participated in several projects and research on maternal and reproductive health, with special research interest in racial/ethical disparities.
- Responsibilities included: managing and contributing to project designs; participating in field studies and data quality control; conducting literature reviews, data analysis, and writing reports; producing presentations.
- Contributed to writing research papers for publication: 4 published, 2 under review, 3 awaiting submission.

- Select projects:
    - The External Evaluation for UNICEF “Maternal and Child Health and Development" Project (baseline, midterm and final survey)
    - Inequalities of maternal and child outcomes and racial disparities in 42 counties in Western China
    - Geographical and sociodemographic inequalities of HBV in 16 million childbearing-age women in China
    - Maternal folic acid level and children 's cognitive function development

Department of Global Health/ Social Medicine, Peking University **2013 – 2015**

Research Assistant

- Engaged in the National College Students Reproductive Health Project, including writing proposal, designing data collect tool, and setting monitoring and evaluation plan. The result was used by UNFPA and other organizations as a reference for designing youth reproductive health programs.
- Conducted a pilot study on the effect of dormitory environment and culture on college students’ sleeping quality.

College Innovation Research and Training Program, Peking University **2013 – 2014**

Internal Team Coordinator

- Led research on flour food exposure to aluminum and analyzed students’ dietary aluminum exposure.
- Took charge of the whole process, including designing, sampling, statistics analysis and result publishing.
- Won 1st place among all teams, 1 peer-reviewed article was published.

PROFESSIONAL EXPERIENCE

United Nations International Children's Emergency Fund (UNICEF), Beijing **Jun-Aug 2017**

Maternal & Child Project Analyst Intern

- Used STATA to perform data cleaning for a program monitoring data and statistical analysis for 3 peer-reviewed MCH research articles.
- Developed final reports for program evaluation of three child development promotion projects in western China and translated an 80-page project document from Chinese into English.

Center for Communication Programs, John Hopkins University **Mar-Jun 2017**

Indicator Bank Intern

- Developed a searchable electronic database for program performance indicators that will be used in further monitoring and evaluations for communication and behavior change programs in developing countries.

Center for Disease Prevention and Control, Beijing **Jul-Sep 2015**

Summer Intern (Rotational)

- Analyzed the effect and cost-effectiveness of a self-management of diabetes intervention trial.
- Collected data and controlled quality for local infectious disease surveillance.
- Completed routine tests of microclimate and water quality at 10 local shopping malls.

Peking University 9th Affiliated Hospital, Beijing **2014 – 2015**

Medical Intern (Rotational)

- Provided routine medical care, gained insight in clinical treatments and hospital operations.

TEACHING EXPERIENCE

Epidemiologic Inference in Public Health, Johns Hopkins University **Aug-Oct 2017**

Teaching Assistant

- Gave lectures to students in labs, facilitated discussion group sessions, held office hours.

Principles of Epidemiology, Johns Hopkins University **Jun-Jul 2017**

Teaching Assistant

- Assisted professor during lectures, facilitated discussion group sessions, held office hours three times a week.

Stata Programming, Johns Hopkins University **Mar-May 2018**

Teaching Assistant

- Assisted professor during lectures, held office hours, graded students' Stata coding assignments.

Epidemiologic Practice Methods for Population Health Research, Johns Hopkins University

Teaching Assistant **Mar-May 2018**

- Assisted professor during lectures, facilitated discussion group sessions, prepared Stata and R codes, graded students' assignments.

LEADERSHIP & COMMUNITY SERVICE

Global Health Club, Peking University **2014 – 2016**

Co-founder & President

- Initiated the "*Smoke-Free Is Fashionable*" themed online-video contest with the support of WHO Beijing office.
- Forged a communication platform between international health organizations and Chinese youth.

Asian Liver Center, Stanford University **2013 – 2014**

NGO that spearheads educational outreach and advocacy efforts of hepatitis B prevention and treatment

Project Manager/ Marketing Department

- Developed a health education and vaccination provision program on HBV for factory workers in Suzhou, China.
- Conducted an HBV anti-discrimination campaign aimed at white collar workers, including base and final line surveys, bus advertisements and pamphlet promotions.

Sunshine and Love Free Clinic **2011 – 2016**

Volunteer

- Provided physical examinations to migrant workers without local health insurance.
- Designed a cardiovascular disease prevention brochure for elderly migrants in local communities.

SELECTED PUBLICATIONS (Available upon request)

- **Anqi W.,** Hong Z., Xiaona H., et al. The dietary diversity and stunting prevalence in minority children under 3 years old: a cross-sectional study in forty-two counties of Western China. British Journal of Nutrition. 2017,118, 840–48*;*
- **Anqi, W.**, Kehui, H., Kuoyue, L., et. al. Assessment on the exposure of Aluminum from flour products in canteens of colleges in Beijing & KAP survey on Aluminum food safety of college

students. Chinese Journal of School Health, 2016, 6(2):79-81;

- **Anqi, W.,** Yuhou, Z., Zhaofeng, Z., et. al. Psychological pressure among clinicians at a major hospital in Beijing. Chinese Journal of Social Medicine. 2016, 33(4);
- Wang Y, Zhou H, Zhang L, Zhong Q, Wang Q, Shen H, **Anqi, W.**, et al. Prevalence of chronic hepatitis B and status of HBV care among rural women who planned to conceive in China. Scientific reports. 2017;7(1):12090;
- Long, Z., Yuanyuan, W., Kenrad E. Nelson, **Anqi, W.**, et al. Status of HBsAg seroprevalence in 15 million rural couples in China: a cross-sectional study. Scientific Reports. 2017 Feb 21;7:42822;
- Hong, Z., Long, Z., Ye, F., Huntington D, **Anqi, W**. et al. (2016) The Effect of Maternal Death on the Health of the Husband and Children in a Rural Area of China: A Prospective Cohort Study. PLoS ONE 11(6): e0157122;
- Bang, Z., Kailu, W., Zheng, X., **Anqi, W**., et. al. Effect and Mechanism of Dormitory Environment and Culture on College Students' Sleeping Quality. Chinese Journal of Social Medicine, 2014, 31(6): 419-422.
- Reviewer: *Journal of Obstetrics and Gynaecology*

PROFESSIONAL SKILLS

- Language: English: proficient (spoken and written), Japanese: fluent (spoken and written), Chinese: native
- Computer: Programming (C++, Python), Statistics software (SAS, STATA, R, SPSS), ArcGIS, Office Suites